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Parathyroid hormone and growth in children with chronic renal failure

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Background. In pediatric chronic renal failure (CRF) optimal parathyroid hormone (PTH) concentrations that minimize renal osteodystrophy and maximize growth are unknown. The search for optimum concentrations has been complicated as currently used "intact" PTH (iPTH) assays cross-react with long carboxyl-terminal PTH fragments (C-PTH), which antagonize the biologic actions of 1-84 PTH. The purpose of this study was to investigate the relationship between PTH, the 1-84 PTH:C-PTH ratio and growth rate in children with CRF.

Methods. A total of 162 patients, median (range) age 9.9 years (0.3 to 17.1 years), were recruited: 136 with a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 [96 managed conservatively (CRF group) and 40 transplanted patients], and 26 dialysis patients. Over a median (range) period of 1.1 years (0.5 to 1.7 years), children attended five (three to 15) clinics at which iPTH, cyclase-activating PTH (CAP-PTH), and height were measured.

Results. Mean PTH concentrations were within the normal range for both assays for the CRF group and up to twice the upper limit of normal for the dialysis group; CAP-PTH 24.8 pg/mL and 59.9 pg/mL (normal range 5 to 39 pg/mL), iPTH 37.1 pg/mL, and 102.6 pg/mL, respectively (normal range 14 to 66 pg/mL). The patients grew normally (change in height standard deviation score per year (ΔHtSDS) = −0.01). There was no relationship between PTH concentrations and ΔHtSDS in any patient group. The 1-84 PTH:C-PTH ratio was lower in dialyzed patients ($P = 0.003$), with worsening renal function ($P = 0.047$) and with PTH concentrations outside the normal range ($P = 0.01$). There was a weak correlation between the 1-84 PTH:C-PTH ratio and the ΔHtSDS ($r = 0.2$, $P = 0.01$).

Conclusion. Normal range PTH concentrations are appropriate, allowing normal growth in children with CRF managed conservatively. C-PTH may be of clinical significance.

Key words: chronic renal failure, growth, parathyroid hormone, carboxyl-terminal PTH, renal osteodystrophy.

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Disordered parathyroid hormone (PTH) secretion is frequently encountered in chronic renal failure (CRF), occurs early in the course of the disease and is pivotal to the etiology of renal osteodystrophy [1, 2]. Optimum management of hyperparathyroidism in children, who have a lifetime of inadequate renal function ahead of them, is particularly important because of the potential to affect growth [3, 4] and because hyperparathyroidism is an independent risk factor for cardiovascular disease [5, 6].

In adults, recommendations are for raised PTH concentrations [7] as elevated concentrations have been found to be required to maintain normal bone turnover in dialyzed patients [8]. There is little evidence on which to base recommendations for optimum PTH concentrations in children [9]. Pediatric histologic studies in dialyzed children [10–13] concur with adult data regarding the relationship between PTH concentrations, bone turnover and renal osteodystrophy, but did not investigate or are inconsistent with regard to effects upon growth. In children with CRF prior to dialysis, data investigating the relationship between PTH concentrations and growth are also inconsistent. PTH concentrations have been shown to be positively correlated with growth [14]. However, we have demonstrated catch-up growth with PTH concentrations at the upper limit of the normal range in children with conservatively managed CRF [15].

Explanations of the necessity for supraphysiologic PTH concentrations have been based upon the concept of "skeletal resistance to PTH," the mechanism for which is unclear [16]. One cause may be that current "intact" immunoradiometric (IRMA) PTH assays exhibit cross-reactivity between 1-84 PTH and long carboxyl-terminal PTH (C-PTH) fragments (likely to be 7-84 [17]), resulting in an overestimation of the actual 1-84 PTH concentrations [17–19]. Furthermore, it has been shown that 7-84 PTH has an inhibitory effect upon the biologic actions of 1-84 PTH [20], mediated at a separate C-terminal receptor [21–23]. It is, therefore, possible that C-PTH is implicated in PTH "resistance," which is of particular

importance as C-PTH concentrations increase with worsening CRF [24, 25].

With the introduction of commercial assays [cyclase-activating PTH (CAP-PTH)] (Scantibodies, Inc., San Clemente, CA, USA, and BioIntact PTH, Nichols Institute) that specifically measure only 1-84 PTH [26, 27], evidence for the clinical effects of C-PTH is emerging; in particular the use of the 1-84 PTH:C-PTH ratio as a surrogate marker of bone turnover has been studied in patients on dialysis. However, data relating a low ratio (i.e., a preponderance of 7-84 PTH) with low bone turnover are not consistently reported [28–31]. Further investigation of this ratio is needed [32].

If C-PTH has biologic activity in adults it is also likely to antagonize the actions of 1-84 PTH in children as well. We have previously demonstrated in children with CRF that the relative proportion of C-PTH to 1-84 PTH increases with worsening CRF and also with PTH concentrations outside the normal range [25]. To date the effects, if any, of C-PTH upon growth rate are undetermined. The aim of this study was to investigate the relationship between PTH, the 1-84 PTH:C-PTH ratio and longitudinal growth in children with varying severity of CRF in order to provide evidence for optimal PTH concentrations.

METHODS

Patients

Between July 2001 and March 2003, patients with a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 or on dialysis were recruited from CRF, dialysis, and transplant clinics at Great Ormond Street Hospital. All patients not treated with growth hormone were approached. Routine samples were collected for sodium, potassium, bicarbonate, urea, creatinine, calcium, ionized calcium, magnesium, phosphate, alkaline phosphatase, and albumin. Additional samples were collected for CAP-PTH and intact PTH (iPTH) IRMA assays. Height, weight, and pubertal stage were assessed by trained personnel using standard techniques [33] (i.e., Harpenden stadiometer) and information on medical therapy was collected.

Management of hyperparathyroidism begins in our unit with the measurement of the iPTH concentration when the GFR falls to 70 mL/min/1.73 m^2. The aim has been to try to prevent hyperparathyroidism; unlike many pediatric units, maintaining PTH within the normal range throughout the course of CRF in order to prevent escape of the parathyroid gland from normal control mechanisms. We are able to attempt this as many patients are referred antenatally or early in the course of their disease and because we actively screen children with bilateral renal defects by measurement of GFR by ethylenediaminetetraacetic acid (EDTA) clearance. Treatment begins with dietary phosphate restriction followed by the introduction of calcium carbonate, aiming to maintain the serum phosphate below the 50th centile for age as far as possible with minimal effect on plasma calcium by giving with feeds. If necessary, alfacalcidol is prescribed at the smallest dose to increase serum calcium to a level sufficient to suppress PTH to within the normal range. The study was approved by the local Research and Ethics Committee. Written consent was obtained from parents and, where appropriate, participating adolescents.

Table 1. Plasma concentrations

iPTH represents 1-84 PTH and C-PTH
CAP-PTH represents 1-84 PTH
C-PTH = iPTH − CAP-PTH

Assays

All PTH samples (EDTA plasma) were sent to the laboratory immediately after blood was drawn, centrifuged, and frozen at −70°C for no longer than 4 months before being sent to Scantibodies Clinical Laboratory, Inc. for analysis. Both laboratories were blinded to all clinical data. Plasma 1-84 PTH was determined by the CAP-IRMA using an I-125 radiolabeled detection antibody with a specificity that is dependent on the presence of the first amino acid from the N-terminal site (Whole PTH™) (Scantibodies Laboratory, Inc.). The reference range of the assay in normal individuals is 5 to 39 pg/mL with an assay sensitivity of 1.0 pg/mL and a linear measurement range up to 2100 pg/mL for undiluted patient samples. The intra- and interassay variances are less than 5% and 8%, respectively [26]. The plasma total iPTH value was determined by an IRMA (Scantibodies Laboratory, Inc.), which measured both 1-84 PTH and 7-84 PTH in an equal molar manner [34]. The total iPTH assay showed a detection sensitivity of 1.2 pg/mL and its intra- and interassay variances are of less than 5% and 7%, respectively. Plasma concentrations of C-PTH were determined by subtracting the CAP-PTH value from the result of the iPTH. The 1-84 PTH: C-PTH ratio was then calculated [28] (see Table 1).

Routine biochemistry (urea, creatinine, calcium, phosphate, alkaline phosphatase, and albumin) was measured on a Vitros 750 analyzer (Johnson & Johnson, High Wycombe, UK). Ionized calcium was determined using a Ciba-Corning 634 calcium/pH electrode analyzer and Bayer diagnostic reagents (Bayer Diagnostic Division, Newbury, UK).

Statistics

Data were analyzed using SPSS version 10 (SPSS, Chicago, IL, USA). Measurements that were not normally distributed were log (10) transformed, in order to comply with the assumptions of the statistical methods

Table 2. Demographic data and mean serum biochemical concentrations by patient group

	All patients ($N = 162$)	Chronic renal failure patients ($N = 96$)	Hemodialysis group ($N = 7$)	Peritoneal dialysis group ($N = 19$)	Transplant group ($N = 40$)	P value
Gender male:female%	69:31	70:30	43:57	68:32	70:30	$= 0.52$, χ^2
Age *median years old* (range)	9.9 (0.3–17.1)	6.5 (0.3–16.9)	13.7 (2.8–16.1)	13.2 (5.6–16.9)	13.8 (3.8–17.1)	<0.001, Kruskal-Wallis
Urea *mmol/L* (range)	11.7 (3.7–33.6)	11.1 (3.7–33.6)	21.8 (15.1–27.3)	15.1 (7.9–25.6)	10.5 (4.8–22.3)	<0.001 ANOVA
Creatinine *μmol/L* (range)	184 (35–1186)	145 (35–679)	870 (507–1186)	712 (401–1027)	132 (61–521)	<0.001 ANOVA
Median glomerular filtration rate *mL/min/1.73 m²* (range)		28 (7–60)			38 (13–60)	=0.003 Mann-Whitney

ANOVA is analysis of variance. 95% CI for mean or range (as indicated) in parentheses.

used; these included serum urea and creatinine concentrations and PTH concentrations as measured by both assays and also the 1-84 PTH:C-PTH ratio. Mean values were therefore expressed as geometric means. Mean patient values were calculated for all biochemical markers recorded over the duration of the study period and these data were used to provide an overall summary of the data. Analysis of variance (ANOVA) was used to assess differences between several groups. Although details of each patient group were given in demographic and biochemical tables, the peritoneal and hemodialysis patients, due to small numbers, were grouped together for some analyses.

For skewed distributions, such as GFRs, the Mann-Whitney test was used for comparison between two patient groups. Kruskal-Wallis test was used to compare skewed data, such as age, between more than two patient groups.

Phosphate concentrations are particularly age dependent [35], thus an age-corrected phosphate concentration was calculated by expressing the phosphate concentration as a proportion of the age dependent upper limit of normal.

When investigating growth, standard deviation scores (SDS) were calculated for height and weight using the British 1990 growth reference; this summarizes the anthropometric measures from infancy to adulthood [36]. Changes to these data over the study period were standardized to rate of change of the SDS per year. One sample *t* tests were used to compare SDS values and changes in SDS values with the general population. Pearson correlation coefficients and regression analysis were used to investigate the relationships between biochemical markers, SDS for anthropometric measures and other continuous factors.

RESULTS

In total 162 [111 (69%) male] patients were recruited. There were 96 children with a GFR <60 mL/min/1.73 m^2, managed conservatively (CRF group), 40 renal transplant patients with a GFR <60 mL/min/1.73 m^2 (transplant group), and 19 patients maintained on peritoneal dialysis and seven on hemodialysis (dialysis group). Their underlying diagnoses reflected those of any pediatric CRF program. Data (anthropometric and serum samples) were collected for a median (range) of 1.1 years (0.5 to 1.7 years), at five (three to 15) clinic visits. The median age at inclusion was 9.9 years. However, the CRF group was significantly younger, at 6.5 years (Table 2), compared with other groups, 13.5 years ($P < 0.01$).

Over three fourths (78%) of patients had a formal 51 chromium EDTA (^{51}Cr-EDTA) GFR investigation either within the 18 months prior to commencement or during the course of the research. The Schwartz formula [37] was used to estimate the GFR of the remaining 22% of patients: 26 from the CRF group and four from the transplant group. The median GFR was lower, 28 mL/min/1.73 m^2, in the CRF group than the transplant group, 38 mL/min/1.73 m^2 ($P = 0.003$, Mann-Whitney). Overall mean serum calcium and ionized calcium concentrations were within the normal range and did not differ between patient groups (Table 3). Mean serum phosphate concentrations were 92% of the age-adjusted upper limit of normal range, which represents a value equivalent to about the 75th centile of the age-dependent normal range. The age-adjusted phosphate levels were significantly higher in the dialyzed patients compared to both those with CRF and transplanted patients ($P < 0.002$ post hoc Tamhane's T2). Over the course of the study the mean calcium phosphate product (Ca × P) was 42.4 mg^2/dL^2.

PTH concentrations and the 1-84 PTH:C-PTH ratio

Overall mean iPTH and CAP-PTH values were within their normal ranges (Table 4). The haemodialysis patients had mean iPTH and CAP-PTH concentrations just over two times the upper limits of normal range and patients on peritoneal dialysis had mean values that were about 1.5 times the upper limits of normal range (Table 4). Overall correlation between mean PTH concentrations as measured by the two PTH assays was $r = 0.975$, $P < 0.001$.

In the CRF group there was a weak negative correlation between GFR and iPTH ($r = -0.24$, $P = 0.021$) but correlation with CAP-PTH was not significant ($r = -0.18$, $P = 0.08$). In this CRF group there was also a weak

Table 3. Biochemical summary data for patients throughout the study period

Measurement (normal range)	All Patients ($N = 162$)	Chronic renal failure patients ($N = 96$)	Hemodialysis group ($N = 7$)	Peritoneal dialysis group ($N = 19$)	Transplant group ($N = 40$)	P value (ANOVA)
Hemoglobin *g/dL* (10.0-14.5)	12.1 (8.5-18.2)	12.7 (10.1-18.2)	10.5 (8.5-12.8)	12 (9.3-15)	11.8 (9.6-15.4)	<0.001
Sodium *mmol/L* (135-145)	140 (133-146)	140 (133-144)	139 (135-143)	139 (134-143)	141 (137-146)	0.022
Potassium *mmol/L* (3.5-5.5)	4.3 (3.0-6.1)	4.2 (3.0-5.4)	4.9 (3.6-6.1)	4.1 (3.4-5.1)	4.4 (3.3-5.3)	<0.001
Bicarbonate *mmol/L* (18-26)	24 (18-31)	24 (18-29)	23 (20-26)	26 (21-31)	23 (19-27)	<0.001
Calcium *mmol/L* (2.22-2.74)	2.37 (1.94-2.72)	2.37 (2.03-2.69)	2.35 (2.18-2.52)	2.37 (1.94-2.72)	2.35 (2.21-2.48)	0.77
Ionized calcium *mmol/L* (1.15-1.41)	1.25 (0.99-1.56)	1.26 (1.12-1.52)	1.21 (1.11-1.36)	1.25 (1.01-1.56)	1.25 (0.99-1.34)	0.371
Phosphate[a] Age-adjusted	0.92 (0.46-1.68)	0.89 (0.60-1.46)	1.03 (0.71-0.68)	1.11 (0.80-1.54)	0.87 (0.46-1.16)	<0.001
magnesium *mmol/L* (0.74-1.0)	0.86 (0.59-1.91)	0.85 (0.60-1.31)	1.12 (0.89-1.37)	1.03 (0.63-1.91)	0.73 (0.59-0.92)	<0.001
ALP *U/L* (110-440)	198 (48-1038)	201 (48-454)	337 (80-1038)	199 (69-415)	165 (56-298)	<0.001
Albumin *g/L* (35-55)	39 (31-51)	40 (33-45)	38 (35-40)	36 (31-51)	41 (35-45)	<0.001
Calcium phosphate product mg^2/dL^2	42.4 (19.6-79.3)	43.4 (25.3-79.3)	44.7 (31.8-68.6)	48.2 (35.4-64.2)	37.0 (19.6-47.4)	<0.001

ANOVA is analysis of variance and compares all four patient groups. ALP is alkaline phosphatase. Range of overall summary data in parentheses.
[a]Phosphate expressed as proportion of age adjusted upper limit of normal.

Table 4. Mean parathyroid hormone (PTH) concentrations and 1-84 PTH:carboxy-terminal PTH (C-PTH) ratio by patient group

	All patients ($N = 162$)	Chronic renal failure patients ($N = 96$)	Hemodialysis group ($N = 7$)	Peritoneal dialysis group ($N = 19$)	Transplant group ($N = 40$)	P value ANOVA
iPTH *pg/mL* (14-66 pg/mL)	44.9 (5-596)	37.1 (5-514)	143.7 (42.3-541)	90.7 (10.0-596)	41.3 (15.3-195)	<0.001
CAP-PTH *pg/mL* (5-39 pg/mL)	28.7 (1.7-403)	24.8 (1.7-368)	93.1 (21.2-387)	50.0 (3.0-403)	25.4 (7.0-87)	<0.001
1-84 PTH:C-PTH ratio	2.5 (0.6-45)	3.0 (0.7-45)	2.6 (1.1-7.2)	1.6 (0.6-7.5)	2.0 (1.1-5.6)	<0.001

Abbreviations are: iPTH, intact parthyroid hormone; CAP, cyclase-activating protein. Range of overall summary data in parentheses.

but significant correlation between the GFR and the 1-84 PTH:C-PTH ratio ($r = 0.2$, $P = 0.047$) (i.e., an increase in C-PTH as CRF progresses). Increases in the relative proportion of C-PTH were also found in dialyzed and transplanted patients (Table 4) ($P = 0.03$ and $P < 0.001$, respectively, post hoc Tamhane's T2).

Overall, the ratio was significantly higher in those with normal range CAP-PTH (2.7 compared to 2.1, $P = 0.01$) compared to those with raised CAP-PTH concentrations and in those with normal range iPTH compared to raised iPTH (2.8 compared to 1.9, $P = 0.001$).

Change in height SDS

The height SDS and weight SDS at inclusion were significantly lower than the normal population ($P < 0.001$ for both) (Table 5). The change in these anthropometric measures over the course of the study, expressed as change in height SDS per year (ΔHtSDS) and change in weight SDS (ΔWtSDS) were not different compared with an expected mean change of zero in the normal population ($P = 0.89$ and $P = 0.19$, respectively). ANOVA did not demonstrate any differences in ΔHtSDS between patient groups ($P = 0.19$), nor was there any difference between the genders ($P = 0.49$). When split into three equal groups, dependent upon length of time included in the study, ANOVA did not demonstrate any difference in the ΔHtSDS ($P = 0.19$).

There was no relationship between either iPTH or CAP-PTH concentrations and growth ($r = -0.1$, $P = 0.22$ and $r = -0.06$, $P = 0.46$, respectively).

In the CRF group there was a weak but significant correlation between the ΔHtSDS and the 1-84 PTH: C-PTH ratio ($r = 0.22$, $P = 0.03$). The correlation between ΔHtSDS and the 1-84 PTH:C-PTH ratio persisted when all patients were analyzed together ($r = 0.2$, $P = 0.01$) and the relationship was emphasized by division of all the patients into three groups (tertiles) according to the 1-84 PTH:C-PTH ratio (ANOVA $P = 0.039$); the third of patients with the highest 1-84 PTH:C-PTH ratio grew better than those with the lowest ratio (ΔHtSDS = 0.086 (95% CI −0.012 to +0.184) versus −0.086 (95% CI −0.165 to −0.007) ($P = 0.033$).

Enteral feeds

Twenty-eight (17%) of the patients were fed entirely or supplemented via gastrostomy feeding tubes. Seventeen were in the CRF group, 10 in the dialysis group, and one patient was in the transplant group; patients in the dialysis group were more likely to have a gastrostomy ($P = 0.002$, chi-square).

As failure to thrive is an indication for employing this modality of therapy, this group of artificially fed patients were smaller; height SDS −1.75 compared to −1.20 ($P = 0.028$) and weight SDS −1.10 compared to −0.41 ($P = 0.003$). However, growth rates, ΔHtSDS and ΔWtSDS,

Table 5. Height (Ht) and weight (wt) standard deviation score (SDS) and rate of change by patient group

	All patients ($N = 162$)	P value t-test combined to (normal)	Chronic renal failure group ($N = 96$)	Hemodialysis group ($N = 7$)	Peritoneal dialysis group ($N = 19$)	Transplant group ($N = 40$)	P value ANOVA
HtSDS	−1.27	$P < 0.001$	−1.26	−1.72	−1.48	−1.23	0.068
at inclusion	(−4.75-2.27)		(−4.75-2.27)	(−3.18–0.52)	(−3.7-0.71)	(−3.64-0.61)	
ΔHtSDS	0.00	$P = 0.89$	0.04	0.08	−0.10	−0.08	0.19
	(−1.16-1.06)		(−1.16-0.89)	(−0.32–0.84)	(−0.42-0.50)	(−0.58-1.06)	
WtSDS	−0.53	$P < 0.001$	−0.73	−0.58	−0.96	−0.16	0.004
at inclusion	(−4.25-2.94)		(−4.25-2.91)	(−2.71–0.49)	(−2.78-2.3)	(−2.76-2.94)	
ΔWtSDS	0.08	$P = 0.19$	0.16	−0.37	0.17	−0.08	0.12
	(−2.33-2.12)		(−1.72-2.12)	(−1.31–0.59)	(−1.89-1.84)	(−2.33-1.91)	

Analysis of variance (ANOVA) dialysis patients combined.

were not significantly different compared to those fed normally ($P = 0.07$ and $P = 0.35$, respectively).

Puberty

Pubertal assessment was undertaken in those over the age of 9 years old. Ninety-two patients were older than 9 years and of these, 63 (68%) had pubertal assessments (42 boys and 21 girls). No delayed entry into puberty was found. The ΔHtSDS was not different between those who did and those who did not have pubertal assessments ($P = 0.8$).

Prescription of calcium-based phosphate binders and alfacalcidol

One hundred and eight (67%) of the patients were prescribed calcium carbonate. The median (range) dose of prescribed calcium carbonate was 90 mg/kg/day (16 to 692 mg/kg/day).

The prescription of calcium-based phosphate binder was not associated with serum calcium concentrations, age-adjusted serum phosphate concentrations, or PTH concentrations ($P = 0.054$, $P = 0.51$ and $P = 0.83$, respectively); nor was there a relationship with quantities of binder prescribed and the ΔHtSDS ($r = -0.03$, $P = 0.77$). There was, however, a positive correlation between calcium carbonate prescription and the Ca × P product ($r = 0.37$, $P < 0.001$).

The prescription of alfacalcidol was common (93%); the median dose (range) was 12 ng/kg/day (1 to 95 ng/kg/day). There were no relationships between alfacalcidol prescription and serum calcium or age-adjusted phosphate levels, but there was a weak positive correlation with the Ca × P product ($r = 0.18$, $P = 0.028$). The relationship with serum PTH concentrations was weak (CAP-PTH, $r = 0.2$, $P = 0.014$; iPTH, $r = 0.17$, $P = 0.04$).

The quantity of alfacalcidol prescribed was not related to the ΔHtSDS ($r = 0.0$, $P = 0.99$).

Hypercalcemic episodes

During the study period there were five episodes of severe hypercalcaemia (upper limit of reference range plus ∼10% equates to serum calcium >2.95 mmol/L) in five patients prescribed alfacalcidol; three in the CRF group and two on peritoneal dialysis. The frequency of these episodes was equivalent to one episode of severe hypercalcaemia related to alfacalcidol every 36 patient years. In four of the episodes, alfacalcidol was temporarily discontinued but restarted at a lower dose once the hypercalcaemia had resolved, in the fifth case it was not restarted; serum calcium concentrations returned to normal within a few weeks in all cases. One of the CRF patients suffered a significant (>10%) increase in serum creatinine, which returned to baseline following the fall in calcium concentrations. One further episode of severe hypercalcemia was noted in a patient not prescribed alfacalcidol.

DISCUSSION

We have shown that our aim of maintaining normal calcium, phosphate, PTH concentrations and growth rate was achievable using dietary phosphate restriction, calcium-based phosphate binders, and small doses of alfacalcidol in children with CRF. In patients on dialysis, phosphate and PTH were less easy to control, but with PTH concentrations up to twice the upper limit of the normal range growth was normal. There was no correlation between PTH and growth rate, but a higher 1-84PTH:C-PTH ratio was associated with better growth.

The lack of correlation between PTH concentrations (iPTH or CAP-PTH) and growth is consistent with our previous retrospective analysis of children with severe CRF [15]. This is, however, in contrast to one previous study, in 24 prepubertal patients [14], which related improved growth to increased iPTH concentrations, although the authors state that the relationship demonstrated was mainly dependent on the two patients with the highest PTH. Perhaps this difference may be related to patient populations in that our sample includes a large proportion of infants and young children fed with

nasogastric or gastrostomy feeds. There are multiple influences upon growth especially in the face of uremia, in particular nutrition, acidosis, and electrolyte imbalances. These results should be interpreted within the clinical context that strict attention was made to the optimization of nutrition and correction of acidosis and electrolyte imbalances, which undoubtedly underlies much of the growth achieved. It is generally accepted that growth should be measured over at least 12 months to avoid seasonal changes [38]; however, while patients were included for a median of 1.1 years the range was from 0.5 to 1.7 years. Nevertheless, there were no significant differences in the growth rate dependent upon the length of inclusion in the study (i.e., those followed for less than a year grew no differently from those followed for longer).

The concentration of PTH that allows optimum growth is a very important clinical issue, and will depend on both whether the assay selected measures only 1-84 PTH or 1-84 and C-PTH, as well as the severity of CRF. This is because, as we have also shown on cross-sectional data [25], the proportion of C-PTH was higher when PTH concentrations were outside the normal range, which becomes increasingly common as CRF progresses. Furthermore, as in adults, C-PTH concentrations rose as renal function deteriorated [24] so that C-PTH was highest in patients on dialysis [19, 39]. Our results did not reflect the strength of the relationship demonstrated in these adult data, but this is perhaps because the majority of our patients maintained normal range PTH concentrations.

One way of trying to adjust for the relative proportion of active (1-84 PTH) and antagonistic fragments (C-PTH) has been to use the 1-84 PTH:C-PTH ratio. In our patients on dialysis (particularly peritoneal dialysis), the 1-84 PTH:C-PTH ratio was significantly reduced, reflecting a disproportionate increase in C-PTH concentrations compared to 1-84 PTH. This has been previously described in small numbers of adult patients on peritoneal dialysis [19]. It is likely that children and adults on dialysis have the highest concentrations of both PTH and C-PTH, due to the combination of hyperphosphatemic stimulation of PTH secretion, decreased clearance of C-PTH and nonphysiologic changes in serum calcium related to dialysis that may adversely affect the relative proportions of 1-84 PTH and C-PTH secreted.

Although we found no relationship between PTH concentrations and growth rate, there was a positive relationship between the ΔHtSDS and the 1-84 PTH:C-PTH ratio; the 95% CI for the ΔHtSDS for the third of patients with the lowest ratio did not include zero, indicative of suboptimal growth. This relationship does not imply causality (i.e., it cannot be stated that a low ratio will slow growth). Indeed, as concentrations of C-PTH increase with worsening renal function and in dialyzed patients, this relationship may simply be indicative of the effects of worsening uremia on growth. However, given the functional data that C-PTH antagonizes the biologic activity of 1-84 PTH by acting at a receptor separate to the PTH receptor [18, 20, 23], it remains a possibility that increased levels of C-PTH may interfere with bone turnover and consequently play a role in growth retardation. Although normal PTH concentrations allow normal growth in children with conservatively managed CRF, the optimum PTH concentration for patients on dialysis is less clear; dialysis patient numbers were smaller and fewer patients had normal range PTH concentrations. Furthermore, as we do not have bone histology, we are unable to comment upon the affects of our therapeutic management upon bone health and agree with previous suggestions that more research is needed [40–43].

Another important aspect is to establish that no harm is done by encouraging vascular calcification if a policy of strict PTH control is followed; care should be taken to avoid the excessive use of calcium-based phosphate binders and the development of lower turnover renal osteodystrophy [44]. This is because high doses of calcium-based phosphate binders have been associated with vascular calcification [45] and it has recently been demonstrated that therapeutic measures leading to over suppression of the parathyroid gland (parathyroidectomy or excessive calcium load) favor low bone turnover, which may in turn influence arterial calcification [46]. In addition the positive relationship demonstrated between the prescription of calcium-based binders and the Ca × P product, even though relatively weak, is of concern as an increased Ca × P product has been shown to be disadvantageous to long term cardiovascular morbidity and mortality [47] and has been associated with soft tissue calcification [48].

The use of vitamin D therapy is beneficial in altering the natural course of renal osteodystrophy [49]. Indeed the prescription of small doses of alfacalcidol in conjunction with phosphate binders was highly efficacious at controlling PTH concentrations. There appeared to be no detrimental effects of the prescription of alfacalcidol upon growth, although it was occasionally associated with episodes of severe hypercalcemia. Large doses of calcitriol have previously been associated with poor growth in patients on dialysis [11], but conversely, the initial studies in children with CRF found improved growth with low dose 1,25 $(OH)_2$ vitamin D [50]. The infrequent occurrence of severe hypercalcemic episodes, responsive to drug withdrawal, did not appear to have any long-term effects upon renal function, consistent with adult data [49], but it is not known whether these severe hypercalcemic episodes will have had an adverse effect on vascular calcification. Again the positive relationship between drug (alfacalcidol) prescription and Ca × P product is of concern; it may reflect the calcemic effects and/or the use of increased doses in those patients with the poorest

serum PTH and phosphate control. Overall the mean Ca × P product was only 42.2 mg^2/dL^2; the recommended upper limit in adults is 55 mg^2/dL^2 [7, 47]. Thus while calcium-based phosphate binders and alfacalcidol may have potentially deleterious effects upon growth and cardiovascular disease it should be noted that hyperparathyroidism is also a risk factor for cardiovascular morbidity and mortality [5, 51, 52]. Alternatively, other noncalcium-based phosphate binders may be more appropriate at suppressing hyperparathyroidism without the calcium burden [53].

CONCLUSION

Normal growth rate occurs in children with CRF managed conservatively when the PTH (CAP-PTH or iPTH) is within the normal range and with concentrations of up to twice normal in children on dialysis. The role of C-PTH in bone turnover and growth requires further investigation.

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